REMARKS

On page 2 of the Office Action, the Examiner acknowledges Applicants' election of the invention of Group V, i.e., Claims 32-40 (with traverse).

However, the Examiner contends that the restriction is proper and makes the Restriction Requirement final.

Specifically, the Examiner contends that new Claims 21-31 are directed to a method for treating a proliferative disease which requires administration of a *Curcuma* extract in combination with radiation, whereas Claims 32-40 do not require radiation treatment.

Accordingly, Applicants hereby cancel non-elected Claims 21-31 without prejudice to the filing of a Divisional Application thereon.

Also, on page 2 of the Office Action, the Examiner rejects Claims 33-37 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner objects to the phrases "wherein the pharmaceutical composition comprises a *Curcuma* extract" (Claim 33); "wherein the pharmaceutical composition is obtainable by extracting *Curcuma* rhizomes using a solubilizing lipophilic compound" (Claim 35); and "wherein said pharmaceutical composition further comprises an aqueous extract of *Curcuma*" (Claim 37).

As to Claim 33, the Examiner contends that it is unclear whether the pharmaceutical composition comprises one or more *Curcuma* compounds, plus an additional amount of *Curcuma* extract (aqueous/ethanolic) or if the *Curcuma* (aqueous/ethanolic) extracts are defining that there are one or more of the compounds of Claim 32 contained therein.

The Examiner is requested to note that the extracts are meant to define that one or more of the compounds of Claim 32 are contained therein. Thus, Claim 33 is hereby amended to recite such.

As to Claim 35, the Examiner contends that such is confusing with respect to defining the solvent extraction of the herbal plant. Further, the Examiner objects to the expression "obtainable".

In view of the amendments to the claims, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

On page 4 of the Office Action, the Examiner Claims 32-40 under 35 U.S.C. § 102(b) as being anticipated by Bosca et al, Deshpande et al or Quiles et al, as evidenced by Tsuda et al.

Specifically, the Examiner states that each of the cited references teaches the administration of an aqueous alcoholic extract of *Curcuma longa* rhizomes to humans to treat coronary heart disease. Further, the Examiner states that Tsuda et al teaches that elevated plasma fibrinogen is known to progress to atherosclerosis, and thus the *Curcuma longa* extract-administered arteriosclerotic rabbits taught, e.g., by Quiles et al, would inherently be treated with respect to the underlying fibrinogen functional effects as claimed.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

It is may be known that elevated plasma fibrinogen progresses to atherosclerosis, and that such is <u>one</u> of the risk factors for the occurrence of vascular diseases (Tsuda et al, *Atherosclerosis,* <u>122</u> (1996)). However, recently it has been described in the art that there are <u>other</u> risk factors for

cardiovascular diseases such as, reactive protein C, genetic factors, cholesterol, hyperlipoprotinemia, etc. Moreover, different studies have shown that plasma fibrinogen is a risk for cardiovascular diseases, independent of other factors, such as cholesterol, tobacco, obesity, high pressure, diabetes, etc. (see US 2003/0187038; a copy of which is attached hereto).

Specifically, on page 1 paragraph [0002] of US 2003/0187038A1, it is stated that plasma fibrinogen levels (FIB) have been identified as an independent risk factor for cardiovascular diseases. Moreover, in paragraph [0003] it is said that AII antagonistic activity are known to be therapeutic agents for circulatory system diseases such as hypertension, heart diseases, stroke, nephritis, etc. However, no report suggests that compounds with AII antagonistic activity have a fibrinogen-lowering activity.

Tsuda et al corroborates these facts and teaches that while Pravastatin and simvastatin both reduce total cholesterol levels, only Pravastatin reduces fibrinogen levels. That is, simvastatin has no effects on plasma fibrinogen levels. Thus, the skill artisan understands that plasma fibrinogen concentration is an independent parameter in vascular diseases.

Furthermore, as taught by Kannel, *J. Hypertens. Suppl.*, 9(7):S13-9 (1991); a copy of which is attached hereto, an elevated level of fibrinogen increases the risk of cardiovascular disease in both hypertensive and normotensive patients, though the risk is greater at higher blood pressures.

Moreover, as taught in the present application, Vitamin C and Vitamin E, well-known antioxidants and lipidic peroxides reducers, have no effect on plasma concentration of fibrinogen

in humans; and Procubol, which is known to have hypolipemiant activity, increases the plasma fibrinogen concentration.

Therefore, while any drug which is capable of reducing fibrinogen concentration may be useful for treating vascular diseases, the mechanism of action is independent of the mechanism for lowering plasma levels of cholesterol and triglycerides. Moreover, the effect is greater if the plasma fibrinogen is reduced to reference values, according to Tsuda et al, that is 256 mg/dl.

On the other hand, clinical trials with Pravastatin, which may be considered a safe drug, show the existence of adverse effects such as rash, gastrointestinal complaints, musculoskeletal pains and elevations in liver transaminases.

Applicants describe in the patent application different pharmacological activities of *Curcuma* extract: lipidic peroxide reducer activity and high and low density oxidized lipoprotein reducer activity. Lipidic peroxide levels and high and low density oxidized lipoprotein levels, correspond to vascular risk factors but, as discussed above, these risk factors are independent of fibrinogen levels.

The technical effect of the present application is to provide a new use of *Curcuma longa* as a reducer of plasma fibrinogen concentration, i.e., as a reducer of one independent risk factor of vascular diseases.

Another advantage of the present invention is that *Curcuma* extracts provide an unexpectedly greater activity for lowering fibrinogen levels than that of known drugs. Indeed, *Curcuma* extracts can reduce plasma fibrinogen concentrations from pathological values, such 809, 690, 584, 490 mg/dl, to reference values, that is 259 mg/dl.

According to Example 1 of the present application, all fibrinogen values greater than 259 mg/dl were reduced to this value after *Curcuma* extract administration (see Table 1 below):[1/]

Table 1

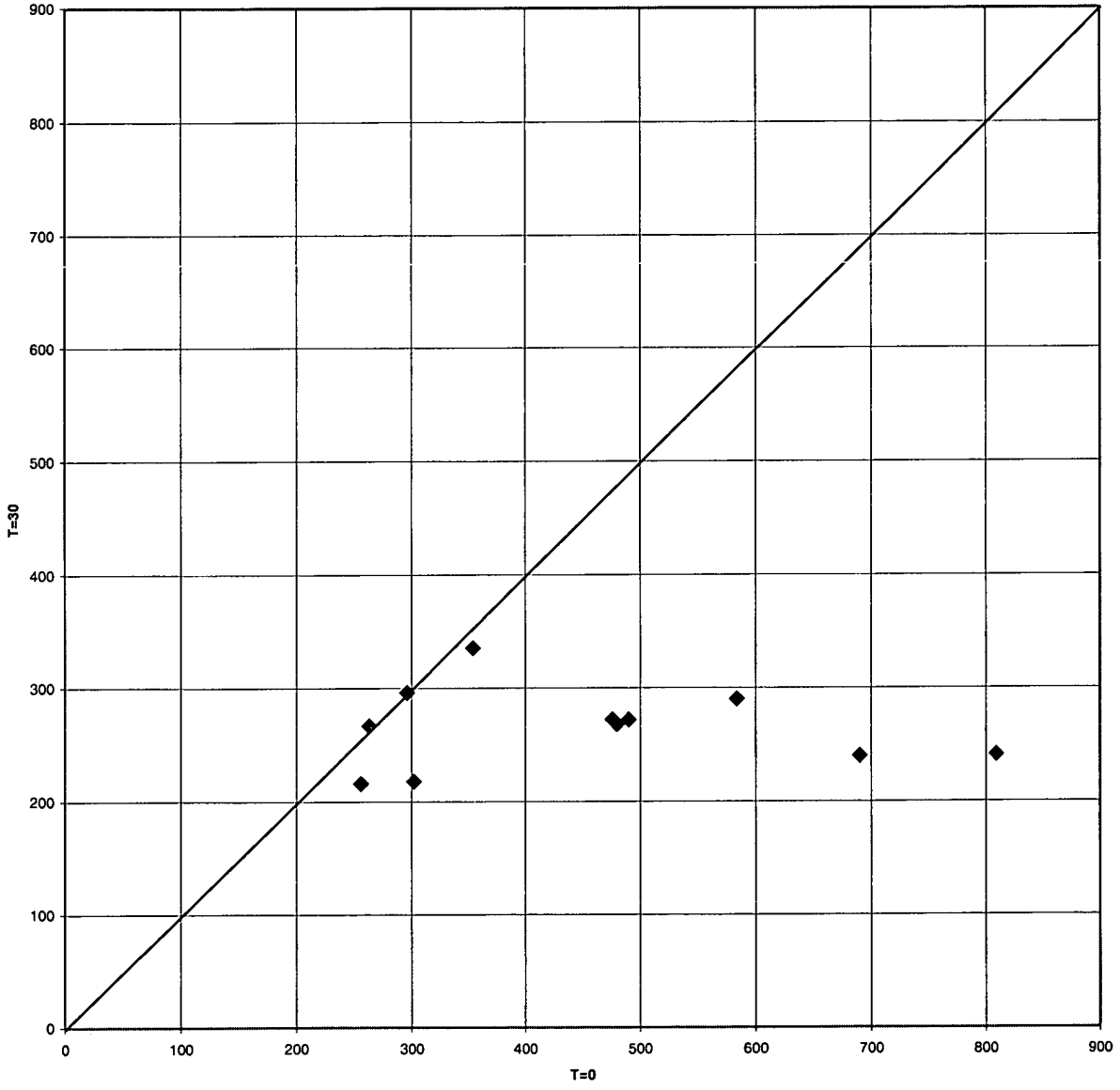
	Plasma fibrinogen concentration in mg/dl at T=0 days	Plasma fibrinogen concentration in mg/dl at T=30 days
	263	267
	256	216
	354	335
	476	272
	302	218
	296	296
	809	241
	480	268
	690	240
	584	290
	490	272
	490	272
Mean	458	266

From Figure 1 below, which corresponds to the values in Table 1, where the X-axis represents the fibrinogen values before the treatment (T=0), and the Y-axis represents the fibrinogen values after the treatment (T=30 days), all of the values are represented below the halving line. Therefore, all of the data show a fibrinogen reduction. Further, all of the data tend to the reference values (259 mg/dl).

[1/] The data in Table 1 corresponds to those values of Table 2 (page 7 of the specification) which at T=0 represent pathological values, that is, a plasma fibrinogen concentration greater than 259 mg/dl.

FIGURE 1

Fibrinogen Concentration on Pathological Values >256



This effect of lowering, and the tendency to the reference values, has been observed analyzing all of the data shown in Example 1 of the present application, for pathological and non-pathological values. The values higher than 259 are reduced, and the values lower than 259 have not shown any

variation. Therefore, another advantage for the *Curcuma* extract is that it represents a fibrinogen modulator without altering other coagulation parameters.

Table 2 (see page 7 of the present specification)

	Plasma fibrinogen concentration in mg/dl at T=0 days	Plasma fibrinogen concentration in mg/dl at T=30 days
	228	215
	263	267
	237	215
	245	272
	173	250
	256	216
	354	335
	220	243
	216	210
	205	221
	226	371
	189	168
	251	282
	216	216
	251	302
	191	191
	476	272
	302	218
	243	187
	207	201
	232	305
	296	296
	809	241
	237	409
	254	267
	480	268
	690	240
	584	290
	490	272
	490	272
Mean	317	257

FIGURE 2

Fibrinogen Values

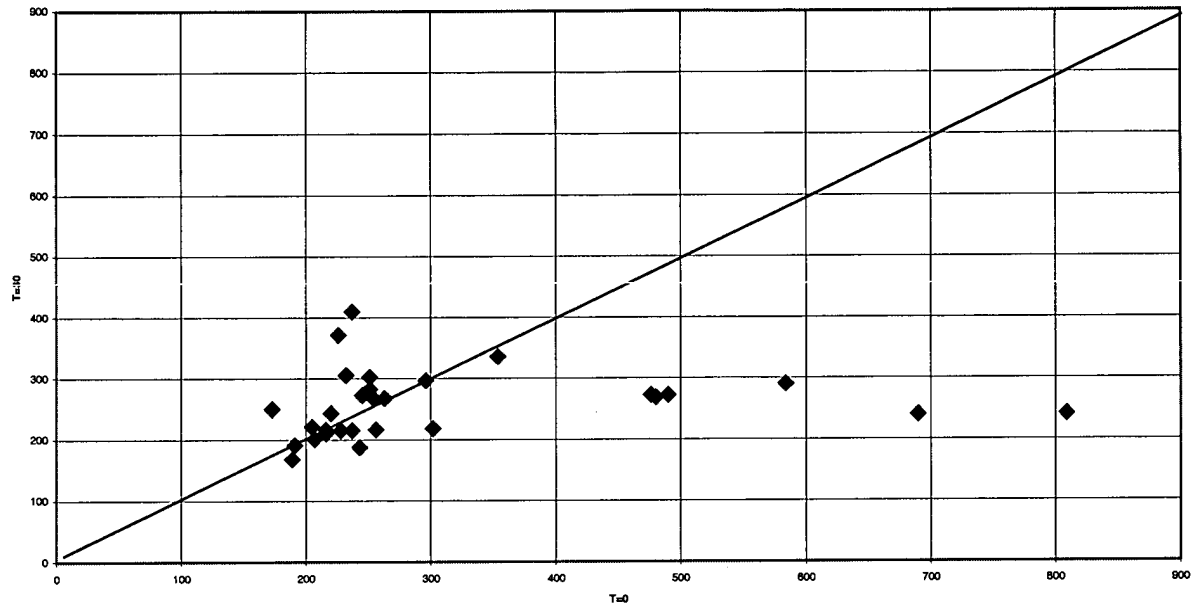


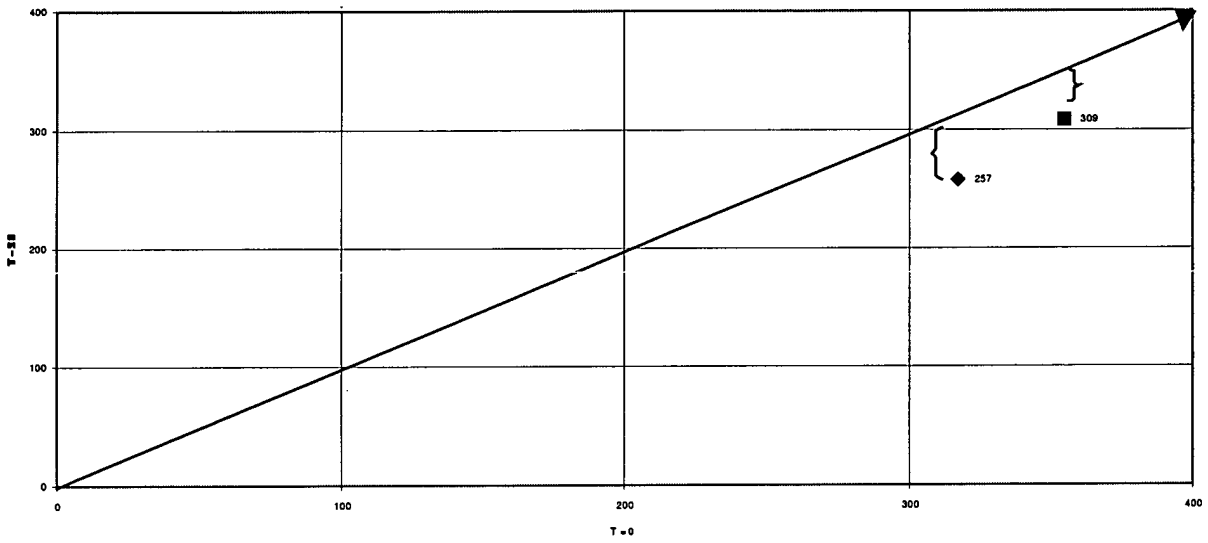
Figure 2 above shows the effects of *Curcuma* extracts on plasma fibrinogen levels, analyzing all of the data disclosed in Example 1 of the present application. Again, after *Curcuma* administration (1 month) the fibrinogen levels were reduced.

Further, another advantage of the present invention, which is not obvious over the prior art, is that *Curcuma* extracts show greater activity than Pravastatin.

In fact, Tsuda et al teaches in Figure 2 thereof, that Pravastatin reduces fibrinogen concentration from 354 mg/dl to 309 mg/dl. Applicants' data show that *Curcuma* extracts reduce fibrinogen from 317 mg/dl to 257 mg/dl, analyzing all of the data disclosed in Example 1.

FIGURE 3

Fibrinogen Reduction (Pravastatin vs. *Curcuma* Extracts)



In Figure 3 above, the fibrinogen reduction after administration of Pravastatin and *Curcuma* extract is compared. The graph consists of two dots: 309 mg/dl & 257 mg/dl.

The dot indicated as 309 mg/dl, represents the mean value of plasma fibrinogen after the treatment with Pravastatin. Before the treatment, the plasma fibrinogen concentration was 354 mg/dl.

The dot indicated by 257 mg/ml, represents the mean value of plasma fibrinogen for patients after treatment with *Curcuma*. Before the treatment, the plasma fibrinogen concentration was 317 mg/dl.

Additionally, the graph shows the halving line.

As can be deduced from the above data, the fibrinogen reduction due to *Curcuma* extract treatment is unexpectedly greater than the reduction due to the treatment with

Pravastatin. The fibrinogen reduction may be calculated measuring the distance between the dots and the halving line.

Furthermore, the final fibrinogen concentration from the patients treated with *Curcuma* are closer to the reference values than the final concentrations in patients treated with Pravastatin.

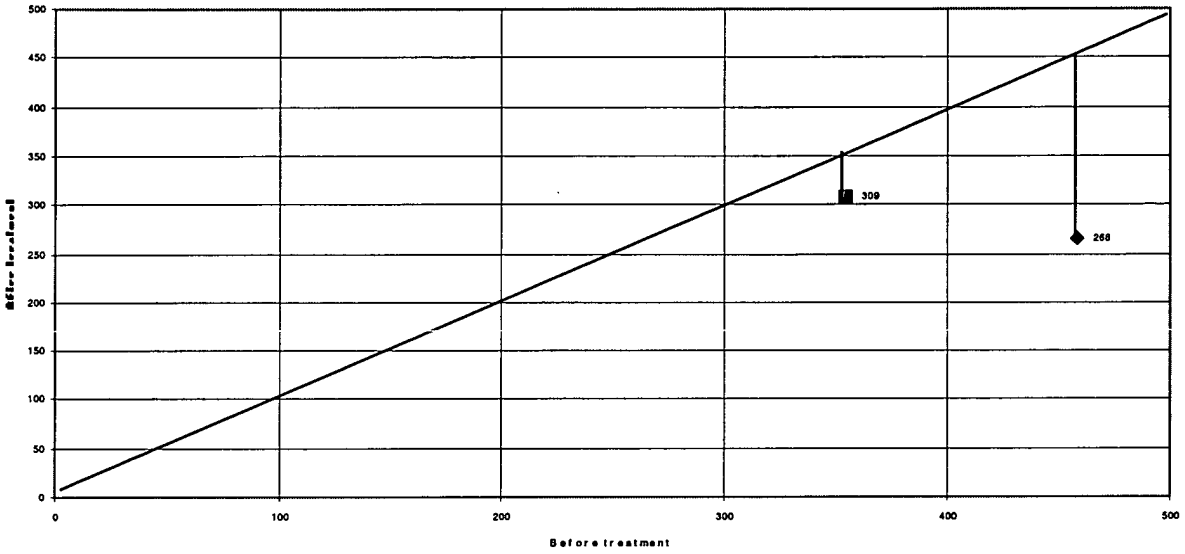
This fact may be deduced by analyzing the mean of pathological values (>259) of *Curcuma* extract versus the mean values of Pravastatin group.

Tsuda et al shows that the fibrinogen concentration before the treatment is 354 mg/dl; and after the treatment is 309 mg/ml.

On the other hand, Applicants found the following fibrinogen concentrations in mg/μl before the treatment: 263, 256, 354, 476, 302, 296, 809, 480, 690, 584, 490, 490, which correspond to pathological values (>259 mg/dl), having a mean of 458.

After *Curcuma* treatment the mean value was 266 mg/dl.

FIGURE 4



In Figure 4 above, it can be observed again that the *Curcuma* extract has greater activity than Pravastatin.

Moreover, another advantage of the present invention is that it provides a means for lowering fibrinogen levels using *Curcuma* extracts without any adverse side-effects, therefore avoiding the adverse side-effects produced by statins (such as Pravastatin).

As mentioned by the Examiner, Tsuda et al indicates that effectively high levels of plasma fibrinogen lead to atherosclerosis.

Quiles et al teaches the use of *Curcuma* administration for lowering the lipid peroxidation in atherosclerotic rabbits, suggesting that active compounds in curcuma extracts may be protective in preventing lipoperoxidation.

Desphande et al discloses the properties of *Curcuma longa* in reducing blood cholesterol and preventing the lipid

peroxidation, thereby avoiding coronary heart diseases by means of these two effects.

On the other hand, Bosca et al expose the powerful antioxidant action of "turmeric", as well as "curcumin" and related phenolic compounds isolated from *Curcuma*, and suggest the use of the *Curcuma* phenolic antioxidants to complement the standard hypolipidemic drugs, administered in the treatment of atherosclerosis. In the experiments in Bosca et al, it is indicated that the levels of peroxidized HDL and LDL are shown therein. In the discussion in Bosca et al, it is taught that in view of the data therein, further work needs to be carried out to investigate the effects of *Curcuma* phenolic antioxidants as co-adjuvants with lipid-lowering drugs in the treatment of hyperlipidemic patients.

All the references cited by the Examiner, that is Tsuda et al, Quiles et al, Desphande et al and Bosca et al, mention the positive effect of administering *Curcuma* to atherosclerotic patients, due to its antioxidant properties or to its capacity of lowering the blood cholesterol, but they do not teach or suggest the effect of *Curcuma* on plasma fibrinogen levels. Considering that US 2003/0187038 indicates that plasma fibrinogen levels constitute an independent risk factor for cardiovascular diseases, it was clearly not obvious, in view of the prior art, that *Curcuma* products would prevent or treat atherosclerosis by modifying the high values of plasma fibrinogen levels.

The differences between prior art and the present invention are summarized as follows:

- Fibrinogen is an independent risk factor in atherosclerosis processes and vascular diseases.

- *Curcuma* extracts reduce fibrinogen levels more than other drugs well-known in the art.
- *Curcuma* extracts reduce fibrinogen levels to references values, while other coagulation parameters are unchanged.
- *Curcuma* extracts have no adverse side effects.

In order to more clearly distinguish the present invention from the cited references, Applicants hereby amend Claim 32 to recite that such is directed to a method of reducing plasma fibrinogen levels in a subject in need thereof.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggest in Bosca et al, Deshpande et al, Quiles et al or Tsuda et al, and thus request withdrawal of the Examiner's rejection.

On page 6 of the Office Action, the Examiner rejects Claims 32-40 under 35 U.S.C. § 103 as being unpatentable over Jackson et al in view of Bosca et al, Deshpande et al and Quiles et al in further view of Tsuda et al.

Specifically, the Examiner states that Jackson et al teaches a pharmaceutical composition containing curcumin as an active ingredient for treating vascular diseases, and that as part of the chain of events leading to the formation of vascular plaques, and narrowing of the vessels, local concentrations of fibrinogen are increased.

Hence, the Examiner concludes that in view of the secondary references, it would have been obvious to administer the curcumin-containing composition taught by Jackson et al to a subject suffering from cardiovascular disease related to elevated fibrinogen levels, as claimed in the present invention.

Further, the Examiner contends that it would have been obvious to administer an ethanolic and/or aqueous ethanolic extract of *Curcuma longa* rhizomes to such a subject in view of the beneficial teachings taught by the secondary references with respect to the use of said extracts because elevated plasma fibrinogen is an inherent phenomenon associated with arteriosclerosis, and administration of curcumin and/or a *Curcuma* extract would intrinsically provide the underlying fibrinogen functional effects claimed.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As discussed above, Bosca et al, Deshpande et al, Quiles et al and Tsuda et al do not provide the deficiencies which exist in Jackson et al.

Jackson et al may disclose a pharmaceutical composition with curcumin (from *Curcuma longa*) as an active ingredient for treating vascular diseases, such as cardiovascular diseases like atherosclerosis. Further, while Jackson et al may indicate that increased local fibrinogen concentrations lead to the formation of atherosclerotic vascular plaques, when they refer to curcumin [0159], Jackson et al indicates curcumin's effect is as a potent antioxidant and its properties as hypolipedemic and hypocholesterolemic.

Therefore, Applicants respectfully submit that it would not have been obvious to one skilled in the art, to administer the curcumin-containing pharmaceutical composition taught by Jackson et al to reduce plasma fibrinogen levels as claimed in the present invention because, although it is well-known in the art that elevated fibrinogen concentrations are a phenomenon associated with the progression of atherosclerosis/cardiovascular

disease, Jackson et al does not teach or suggest that *Curcuma longa* rhizomes can be administered in form of a pharmaceutical composition for reducing the plasma fibrinogen levels, which as discussed above, is an independent risk factor for cardiovascular diseases.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggest in Jackson et al alone, or in view of Bosca et al, Deshpande et al, Quiles et al and Tsuda et al, and thus request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set for above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

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